REMARKS

The Office Action of December 11, 2003 presents the examination of claims 1-6, 8-25, 27-40, 42-86, 89 and 90. These claims remain pending. A minor amendment is made herein to claim 1, to delete the term "characterized by", inadvertently retained in Applicant's last paper.

Rejection under 35 USC § 112, second paragraph

Claims 1-6, 8-21, 74 and 76 stand rejected under 35 USC § 112, second paragraph, as indefinite in the recitation "characterized by". This phrase is deleted from claim 1, as suggested by the Examiner thereby overcoming this rejection without change to the scope of the claim.

Rejection over Carninci 2000

Claims 1-4, 6, 8-23, 27-40, 42-73 and 77-86 stand rejected under 35 USC § 102(a) over Carninci et al. *Genome Research* (2000). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicant has filed (November 19, 2003) a verified English translation of JP 2000-255402, filed August 25, 2000, which is the priority document for the present application. Applicant's Representative understands that the translation did not reach the

Examiner prior to the writing of the present Office Action, but that the translation is now present in the Examiner's file.

It is the further understanding of Applicant's Representative that the English translation of the priority document will prove sufficient to overcome the instant rejection. Review of the translation by the Examiner and withdrawal of the instant rejection are respectfully requested.

Rejection of claims 77-86 for lack of novelty over Carninci 1996

Claims 77-86 remain rejected under 35 USC § 102(b) over Carninci et al. *Genomics* (1996). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner is taking a position that the term "nonspecifically bound to DNA" encompasses digestion of RNA strands that overhang the ends of the first strand synthesized DNA. (See, the "Response to Arguments" at page 13.) This interpretation appears to be consistent with Figure 1 of the present application (note "RNAse I treatment" at the left side). The Examiner also asserts that Applicants are performing the same steps as disclosed in Carninci 1996 for the same purpose and therefore the result of digestion of non-specifically formed RNA-DNA hybrids is inherent.

However, the explanation of Figure 2 provided in the specification, taken with the drawing itself, establishes a different interpretation that "non-specifically bound RNA" actually

refers to hybrids having mismatches along the length of the hybridized segment. It therefore appears that the Examiner is mistaking "non-specifically bound" hybrids for "unbound" (*i.e.*, overhanging) RNA.

The digestion step with RNase I shown in section A of Figure 1 is basically the same as that of Carninci 1996. However, the enzymatic treatment in claims 77-86 iS different from that shown in section A of Figure 1. Rather, claims 77-86 describe treatment of the hybrids, for example RNA/DNA hybrids, with enzyme, as shown in section D of Figure 1 of the present application. This enzymatic treatment is specifically shown in Figure 2 of the present application. As stated in paragraph 0058, page 19 of this application, this enzymatic treatment of the hybrids enables reduction of unintended exclusion of rare cDNA from the rare cDNA library that results from the claimed method.

Another difference between the subject matter of claims 77-86 and Carninci 1996 can be found in the process for preparation of the hybrids. The hybrids in claims 77-86 are those obtained by hybridization of testers with drivers, which may be a product of normalization and/or subtraction, for example as claimed in claims 80-82. On the other hand, the hybrids of DNA and RNA of Carninci 1996 are prepared by synthesis of cDNA with reverse transcriptase, nucleotide substrates of the reverse transcriptase and RNA strands

as templates. Thus, claims 80-82 at least are patentable over Carninci 1996 for this other, or additional, reason as well.

Rejection for obviousness over Chang in view of Carninci 1996

Claims 1-6, 8-25, 27-40, 42-73, 77-86, 89 and 90 stand rejected under 35 USC § 103(a) as being unpatentable over Chang '874 in view of Carninci *Genomics* (1996). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner states at page 6 of the Office Action (page 6) that Chang teaches a desire to remove residual single stranded mRNA (column 24, lines 42-43) but does not teach use of an enzyme.

It is true that Chang teaches a desire to remove residual single stranded mRNA (column 24, lines 42-43). However, the single stranded mRNA to be removed in Chang is mRNA used as a template for cDNA synthesis that remains in the form of free mRNA. Chang does not mention removal of any single stranded RNA that fails to form a RNA/DNA hybrid.

Chang teaches neither deletion of RNA/DNA hybrids of which RNA strands overhang the end of the synthesized DNA strand as shown in Carninci 1996, nor deletion of RNA/DNA hybrids of which RNA is "nonspecifically bound to DNA" like the present invention.

On the other hand, Carninci 1996 never teaches deletion of mRNA templates remaining as free mRNA and not forming a RNA/DNA hybrid. Thus, the Examiner has not established any motivation to

combine the references in the manner suggested. There is no motivation to modify the use the enzymatic treatment of Chang for removal of overhanging single strands of RNA/DNA hybrids or of RNA nonspecifically bound to DNA.

Even if the references are combined in the manner suggested by the Examiner, the result is an invention in which the enzymic treatment of Carninci 1996 is used for the deletion of mRNA templates in Chang. On the other hand, the process of the present invention is not inferred because the hybrids subjected to the enzymic treatment in the present invention are different from those of Chang and Carninci 1996 as mentioned above. That is, the nucleic acids that are digested by the combination of Chang with Carninci 1996 are unbound, overhanging strand portions of hybrids. On the other hand, in the instant invention the digested nucleic acids are those in which there are mismatches along the length of the hybridized segments.

Therefore, the combination of Chang and Carninci 1996 fails to establish *prima facie* obviousness of the invention described by claims 1-6, 8-25, 27-40, 42-73, 77-86, 89 and 90, and the instant rejection should be withdrawn for this reason.

The Examiner further states at page 6 of the Office Action that Chang also teaches that full length clones are desired (column 25, lines 35-38, column 8), but Chang does not teach a protocol to ensure that full length clones are synthesized.

If Carninci 1996 is combined with Chang in the manner suggested by the Examiner, then the technology taught in Carninci 1996 is used for preparation of the first stranded DNA, tester DNA, and indeed full length clones will be obtainable. However, the process described by claim 8 is one in which an enzyme is used to cleave single strand RNA driver nonspecifically bound to single stranded cDNA and the cleaved RNA driver is removed. Thus, even if Chang is combined with Carninci 1996 in the manner suggested by the Examiner, the process of claim 8 is not inferred. Thus, at least the process of claim 8, and claims dependent thereon, is not rendered *prima facie* obvious by the combination of Chang and Carninci 1996. Accordingly, the instant rejection should be withdrawn at least as to claim 8.

With respect to new claim 89, the Examiner's argument that the choice of R_0T value, "depends upon the nucleic acid population being measured, not upon the method of analysis", is not understood. Claim 89 is directed to a method of library construction, not to a method of measurement. Applicant submits that there is no motivation provided by the cited references or the prior art to perform the subtraction and normalization hybridizations at the R_0T values stated in claim 89.

The Examiner did not specifically address claim 90. This claim at least is unobvious over the cited references in view of the unexpected results shown in Figure 6 and described at pages 35-

36 (Example 3) and at page 8 of the specification. It is seen from this disclosure that performing the biotinylation on ice results in a driver preparation that is effective in removing 100% of the undesired cDNA from a library. This result is not predicted by the skilled artisan who reads Chang and Carninci (1996) and accordingly, at least claim 90 should be patentable over these references.

At least claim 8 is also patentable over Chang and Carninci (1996). The invention of claim 8 also provides a result that is unexpected by the skilled artisan in view of these references. The data in Table 2 on page 42 show that digestion of the non-specific cDNA-RNA hybrids results in unexpected improvement in the percentage of unique clones obtained in a normalized/subtracted cDNA library. Accordingly, at least claim 8-11, and claims 27-30, 42-45 and 56 and 64-65 dependent therefrom, which recite the same step, should be found patentable over the Chang and Carninci (1996) references.

Rejections for obviousness over Chang and Carninci (1996) and additional references

Claim 74 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Chang and Carninci (1996) in view of Bouma '242. Claim 75 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Chang and Carninci (1996) in view of Mishra '954. Claim 76 is

rejected under 35 U.S.C. § 103(a) as being unpatentable over Chang and Carninci (1996) in view of Lavery '548. These rejections are respectfully traversed. Reconsideration and withdrawal thereof are requested.

For the reasons above, the combination of Chang and Carninci (1996) fails to establish *prima facie* obviousness of the invention described by claim 1, from which claims 74-76 ultimately depend. The additional references cited for the additional features of claims 74, 75 or 76 do not remedy the failure of the primary and secondary references to disclose or suggest the fundamental aspects of the invention as described by claim 1. Accordingly, each of the above rejections fails for the same reason the rejection of claim 1 fails and so they should be withdrawn.

Applicant submits that the present application well-describes and claims patentable subject matter. The favorable actions of withdrawal of the standing rejections and allowance of the claims are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a two (2) month extension of time for filing a response in connection with the present application. The required fee of $420.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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